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(d) optionally repeating steps (b) through (c) using one or more alternative chemicals to be screened,

wherein a colony of cells which expresses said reporter gene comprises a gene that encodes a protein that together with said screened chemical interacts with said co-regulatory peptidic molecule.

REMARKS

The finality of the previous Office Action, mailed August 13, 1999, has been withdrawn by the Office. The amendment under 37 C.F.R. § 1.116, paper no. 10, has been entered. Claims 44-51 and 53-55 are currently pending in this application.

Claims 44-51 and 53-55 have been rejected under 35 U.S.C. § 101 on the grounds that the claimed invention is not supported by either a credible asserted utility or a well established utility. The Office states that the application discloses a nuclear receptor co-regulatory protein that is capable of binding to a nuclear receptor or nuclear receptor binding domain and that comprises the sequence of SEQ ID NOS:5, 8 or 9, but does not disclose the function of the nuclear receptor co-regulatory protein or its relationship to any disease. It is the Office's position that the main utility of the protein is to carry out research to identify the biological function of the nuclear receptor co-regulatory protein. Applicants respectfully add that the claims of the invention are not drawn to the disclosed nuclear receptor co-regulatory protein itself, but to an assay method that can identify nuclear receptor ligands which interact with the nuclear receptor co-regulatory protein. The Office's position is that the methods claimed do not possess a substantial utility ("real world" use) which is apparent without further confirmation, since the protein itself does not possess such a utility.

Applicants have included with this response a declaration under 37 C.F.R. § 1.132 by Dr. Shiuan Chen, ("Chen Declaration") one of the inventors named on this application. Dr. Chen explains in his declaration how and why the application possesses an asserted utility and a well-established utility, and why the application is enabled in the full scope of the amended claims.

The assay methods of the present invention are designed to screen for compounds that affect nuclear hormone receptors such as the estrogen receptor. Chen Declaration ¶ 4. The co-regulatory protein (such as the proline-rich nuclear receptor co-regulatory protein (PNRC)) effectively is a reagent in the assay system since the PNRC is a component of the responsive functional unit which forms the basis of the assay technique. Chen Declaration ¶ 4. Nuclear receptors are known to play an important role in disease which is well established in the art and establishes a utility for the assay and for the products which are screened in the assay. Chen Declaration ¶ 4. This is and was well known and accepted in the art (see, for example, Jordan, Endocrin. Metab. 10(8):312-317, 1999; Bentrem, Oncol. Res. 11(9):401-407, 1999; Levenson, Eur. J Cancer 35(14):1974-1985, 1999). Chen Declaration ¶ 4. For example, through binding to estrogen, ER (estrogen receptor) plays a critical role in breast cancer development. Antagonists of ER (e.g., tamoxifen) are used as drugs to treat breast cancer. Chen Declaration ¶ 4. An embodiment of the assay method of the invention, in which the proline-rich nuclear receptor co-regulatory protein was used to screen the estrogen receptor, was able to identify Tamoxifen as a potent inhibitor of estradiol (E2) binding to the estrogen receptor (see Figure 1). Chen Declaration ¶ 4. This assay also has identified several new chemical compounds such as ICI 182780, which is exemplified in Figure 1 (attached hereto). Chen Declaration ¶ 4. These new compounds demonstrate potent Tamoxifen-like activity. Chen Declaration ¶ 4. Thus the assay has the utility of identifying compounds which can be used to treat breast cancer. Chen Declaration ¶ 4. This "real-world" utility would be accepted and recognized by the person of skill in the art. Chen Declaration ¶ 4.

This type of assay and the utility thereof is discussed in the specification at page 9, line 24 - page 10, line 11, providing a asserted utility as well as a well-established utility. Chen Declaration ¶ 5. The specification also discusses the utility of the claimed assay in the context of screening for proteins that interact with cancer drugs such as Tamoxifen, causing chemotherapeutic resistance in breast cancer. Chen Declaration ¶ 5. See specification at page 10, line 24 to page 11, line 4. Chen Declaration ¶ 5. Such

a utility also is both specific and well-established, and provides a second asserted and well-established utility. Chen Declaration ¶ 5.

Many other nuclear receptors are known in the art and have been established to play a role in disease. Chen Declaration ¶ 6. Chemical entities which bind to and affect any of these known nuclear receptors may be identified by the assays which are disclosed in the present application. Chen Declaration ¶ 6. Thus, any nuclear receptor may be screened for protein/chemical pairs which modulate its activity. Chen Declaration ¶ 6. The screen is not merely, as the Office asserts, a method of finding proteins which can be used to research functions of nuclear receptors. Chen Declaration ¶ 6. The screen identifies compounds which can modulate the actions of the receptors that have well-established function in the body's physiology. Chen Declaration ¶ 6.

Applicants therefore submit that the claims of the invention fully comply with the utility standards of 35 U.S.C. § 101 and request that the rejection of the claims be withdrawn.

Claims 44-51 and 53-55 have been rejected under 35 U.S.C. § 112, first paragraph on the grounds that they are not supported by a credible asserted utility or a well-established utility. Applicants have discussed above why the claims are fully supported by both a credible asserted utility and a well-established utility. Applicants therefore respectfully submit that this rejection also should be withdrawn.

The Office has further rejected these claims under 35 U.S.C. § 112, first paragraph on the grounds that because the claims encompass any protein having the sequence of SEQ ID NOS:5 or 9, the full scope of the claims is not supported by an enabling disclosure or by sufficient written disclosure to reasonably convey to the skilled person that the inventor had possession of the claimed invention. Although Applicants disagree with this position for the reasons of record, Applicants have amended the claims to recite the sequences of SEQ ID NO: 5, 8 or 9 to further prosecution of this application. Applicants submit that this amendment overcomes the rejection of these claims and respectfully request that it be withdrawn.

The Office also states that the claims lack sufficient written description under 35 U.S.C. § 112, first paragraph because the specification does not sufficiently describe structural characteristics or properties of the chemical species to be screened. Chen Declaration ¶ 7. Applicants have explained that the claimed method is an assay for screening the chemicals. Chen Declaration ¶ 7. Any chemical may be screened. Chen Declaration ¶ 7. Any library of chemicals may be screened. Chen Declaration ¶ 7. The structure of the chemical is not at all relevant to the method and the property of the chemicals is what is being screened, for example binding as known ligands bind or inhibiting binding of known ligands. Chen Declaration ¶ 7.

The "chemicals" listed by the Office at page 4 of the pending office action as representative of chemicals encompassed by the claims are chemicals which are already known to act as ligands. Chen Declaration ¶ 8. The Office therefore appears to conclude that the screening assay method is or should be limited to screening chemicals ready known to bind. Chen Declaration ¶ 8. The method is designed to identify chemicals which were previously not known to bind, not merely to confirm the receptor interactions of known ligands. Chen Declaration ¶ 8.

A person of skill in the art is familiar enough with screening assays to recognize that the value of a screening assay lies it its ability to screen any compound. Chen Declaration ¶ 9. Not all compounds yield a positive result in screens, but a screen is not unsupported by written description merely because all chemicals or classes of chemicals to be identified by the screen are not pre-identified and recited in the claims. Chen Declaration ¶ 9. Nor need the chemicals to be screened be defined by particular structural or functional characteristics. Chen Declaration ¶ 9. It is the screening method itself which allows one to determine the important structural and functional characteristics of the ligand-candidates. Chen Declaration ¶ 9.

Any chemical may be a ligand candidate for a nuclear receptor, regardless of structure, known function or lack of known function. Chen Declaration ¶ 10. Indeed, many or most of chemicals which a person of skill might wish to screen by the claimed assay will have no known functional property at all, and could have any structure. Chen Declaration ¶ 10. The method itself will determine whether the chemical has the

necessary structural property to bind to the nuclear receptors being assayed. Chen Declaration ¶ 10. Therefore it is not possible or desirable to pre-determine which chemicals or chemical classes will be screened for activity by the claimed method. Chen Declaration ¶ 10. If it were possible to know which chemicals productively interacted with nuclear receptors before screening, no screens would be necessary and all possible nuclear receptor ligands would already have been identified. Chen Declaration ¶ 10. However, this clearly is not the case.

As with any screen, if only chemicals already known to interact with nuclear receptors were to be considered for screening, there would be no reason to screen the samples. Chen Declaration ¶ 11. The point of the screening is to determine whether or not there is an interaction with a particular chemical. Chen Declaration ¶ 11. Thus, a negative result in the screen does not mean that the screen does not work for its intended function. Chen Declaration ¶ 11. Any chemical can be screened because whether a particular chemical yields a positive or negative result does not affect whether the screen can be performed or is useful. Chen Declaration ¶ 11. The claims are not drawn to a method of assaying only samples which interact but to determine whether there is an interaction or not with a particular sample. Chen Declaration ¶ 11. Also, since it is never possible to pre-determine which sample will give a positive (or negative) result in any screening assay, the type of disclosure the Office seems to be requiring regarding chemicals to be screened simply can never be available, for any screening method. Chen Declaration ¶ 11. Applicants therefore respectfully submit that a requirement for this disclosure is not proper since Applicants clearly were in possession of the screening assay and have described it in terms sufficient to enable the skilled person to perform the screen. Chen Declaration ¶ 11.

Applicants submit that the claims are fully described and enabled in their entire scope and request that the rejection under 35 U.S.C. § 112, first paragraph be withdrawn.

In view of the foregoing amendments and remarks, the claims are believed to be in condition for allowance. Favorable action is earnestly solicited.

RESPECTFULLY SUBMITTED,			
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Attachments: Mark up of Claims

2124-311.am4

Mark-up of Claims:

53. (Amended) A method for screening for a protein and a chemical, wherein said protein and said chemical together interact with a nuclear receptor co-regulatory [protein that (1) is capable of binding to a nuclear receptor or to a nuclear receptor ligand binding domain and (2) has a region] peptidic molecule according to SEQ ID NO: 5, 8 or 9, wherein said method comprises:

(a) cotransfecting cells with

(i) a library of nucleic acids which encode said proteins to be screened,

(ii) a gene that encodes said co-regulatory [protein] peptidic molecule, and

(iii) a reporter gene the expression of which depends upon said co-regulatory [protein] peptidic molecule binding to said nuclear receptor or said nuclear receptor ligand binding domain

to produce a library of cells which express a library of proteins to be screened and said co-regulatory [protein] peptidic molecule;

(b) growing a first portion of said cotransfected cells in the presence of said chemical to be screened;

(c) growing a second portion of said cotransfected cells in the absence of said chemical to be screened, wherein said second portion is a replicate of said first portion,

(d) comparing the level of expression of said reporter gene in [individual colonies of] cells of said first portion and said second portion; and

(e) optionally repeating steps (b) through (d) using one or more alternative chemicals to be screened,

wherein if [a colony] cells of said first portion of cells [expresses] express said [receptor] reporter gene at a higher level than cells of its corresponding replicate [colony of] in said second portion of cells, then said [colony comprises a gene that encodes a] screened protein [that] together with said screened chemical interacts with said co-regulatory [protein] peptidic molecule.

55. (Amended) A method for screening for a protein and a chemical, wherein said protein and said chemical together interact with a nuclear receptor co-regulatory [protein that (1) is capable of binding to a nuclear receptor or to a nuclear receptor ligand binding domain and (2) has a region] peptidic molecule according to SEQ ID NO: 5, 8 or 9, wherein said method comprises:

(a) cotransfecting cells with

(i) a library of nucleic acids which encode said proteins to be screened,

(ii) a gene that encodes said co-regulatory [protein] peptidic molecule, and

(iii) a reporter gene the expression of which depends upon said co-regulatory [protein] peptidic molecule binding to said nuclear receptor or said nuclear receptor ligand binding domain

to produce a library of cells which express a library of proteins to be screened and said co-regulatory [protein] peptidic molecule;

(b) growing colonies of said cotransfected cells in the presence of said chemical to be screened;

(c) determining the level of expression of said reporter gene in individual colonies of said cotransfected cells; and

(d) optionally repeating steps (b) through [(©)] (c) using one or more alternative chemicals to be screened,

wherein a colony of cells which expresses said [receptor] reporter gene comprises a gene that encodes a protein that together with said screened chemical interacts with said co-regulatory [protein] peptidic molecule.